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APPELLANT'S BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	STAN-352
	Confirmation No.	1829
	First Named Inventor	Kao, Peter N.
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	Group Art Unit	1614
	Examiner Name	Kwon, Brian Yong S
	Title:	"USE OF ANTIPROLIFERATIVE AGENTS IN THE TREATMENT AND PREVENTION OF PULMONARY PROLIFERATIVE VASCULAR DISEASES"

Sir:

This Brief is filed in support of the Applicant's appeal of the Final Rejection dated May 16, 2007. No claims have been allowed. Claims 1, 3-8, 10, 12-13, 19-24, 30, 32-33, 37 and 39 are pending and are appealed. A Notice of Appeal was filed on November 16, 2007. As such this Appeal Brief is timely filed.

The Board of Patent Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. § 134(a).

The Commissioner is hereby authorized to charge deposit account number 50-0815, order number STAN-352 to cover any required fee for filing the Applicant's brief. Additionally, in the event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, the Applicant petitions for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to the above disclosed deposit account.

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REAL PARTY IN INTEREST

The real party in interest in this appeal is The Board of Trustees of the Leland Stanford Junior University.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to the Appellant, the undersigned Appellant's representative, or the assignee to whom the inventor assigned his rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

Claims 1, 3-8, 10, 12-13, 19-24, 30, 32-33, 37 and 39 are pending and are appealed herein. Claims 2, 9, 11, 14-18, 25-29, 31, 34-36 and 38 were cancelled during the prosecution of the application.

STATUS OF AMENDMENTS

Subsequent to issuance of the final Office Action, the Appellants proposed amendments to claims 3, 23, 33 and 37. These amendments were entered by the Examiner. The claims appealed herein contain the amendments.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 recites a method of treating a lung proliferative vascular disorder in a patient by administering an HMG-CoA reductase inhibitor, wherein the HMG-CoA reductase inhibitor is present in an amount that is effective to reduce vascular occlusion in the pulmonary arteries of the patient but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient; the lung proliferative vascular disorder being selected from the group consisting of primary pulmonary hypertension, secondary pulmonary hypertension, Eisenmenger's syndrome, chronic thromboembolic disease, pulmonary fibrosis, obliterative bronchiolitis, and lymphangioleiomyomatosis (See specification page 4, lines 16-24).

Independent claim 3 is directed to a method of treating primary pulmonary hypertension in a patient by administering an HMG-CoA reductase inhibitor in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier at a dose of from about 0.1 to about 100 mg/kg per day, this formulation further comprises the inhibitor in an amount that is effective to

reduce vascular occlusion in the pulmonary arteries of the patient but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient (See specification page 4, lines 26-27).

Independent claim 23 recites a method of treating a primary pulmonary hypertension in a patient by administering an HMG-CoA reductase inhibitor in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier suitable for pulmonary delivery at a dose of from about 0.1 to about 100 mg/kg per day, this formulation further comprises in an amount that is effective to reduce vascular occlusion in the pulmonary arteries of the patient but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient, where the HMG-CoA reductase inhibitor is administered by inhalation (See specification page 6, lines 7-8).

Independent claim 30 recites a method for reversing right ventricular hypertrophy in a patient suffering from pulmonary hypertension by administering an HMG-CoA reductase inhibitor (See specification page 13, lines 27-29).

Independent claim 37 recites a method of treating a primary pulmonary hypertension in a patient by administering simvastatin in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier suitable for pulmonary delivery at a dose of from about 0.1 to about 100 mg/kg per day, wherein the formulation further comprises in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient, wherein the simvastatin is administered by inhalation (See specification page 4, line 26, page 6, lines 7-11).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Appellants request review of the grounds for the rejection of Claims 1, 3-8, 10, 12-13 and 19-24 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which the Applicants regard as their invention.

The Appellants request review of the grounds for the rejection of Claims 1, 3-8, 10, 12, 19-22, 30, 32-33 and 39 under 35 U.S.C. § 102 (b) as being unpatentable over Liao et al. (WO00/56403).

The Appellants request review of the grounds for the rejection of Claims 13, 23-24 and 36-37 under 35 U.S.C. § 103 (a) as being unpatentable over Liao et al. (WO00/56403).

ARGUMENT

Appellants note that for rejections made over the prior art reference Liao *et al.*, the present claims may be grouped separately.

Group I, Claim 1 and the claims dependent thereupon, i.e. Claims 4-8, 10, 12-13 and 19-22 are directed to methods of treating a lung proliferative disorder by administering an HMG-CoA reductase inhibitor.

Group II, Claim 3 is specifically directed to treating primary pulmonary hypertension in a patient.

Group III, Claim 23 and the claim dependent thereupon, i.e. Claim 24, are directed to methods of treating a primary pulmonary hypertension by administering an HMG-CoA reductase inhibitor by inhalation.

Group IV, Claim 30 and the claims dependent thereupon, i.e. Claims 32, 33, and 39 are directed to a method of reversing right ventricular hypertrophy in a patient suffering from pulmonary hypertension by administering an HMG-CoA reductase inhibitor.

Group V, Claim 37 is directed to methods of treating a primary pulmonary hypertension by administering simvastatin by inhalation.

For rejections made under 35 U.S.C. 112, second paragraph, claims 1, 3-8, 10, 12-13 and 19-24 are subject to the rejection, and claims 30, 32-33, 37 and 39 are free of the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3-8, 10, 12-13 and 19-24 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which the Appellants regard as their invention.

According to the M.P.E.P. § 2173.02, in reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent.

The Examiner asserts that Claim 1's recitation of "which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient," renders the claims indefinite. The Examiner asserts that the specification does not provide a standard for this element and that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The Appellants, however, disagree. At page 10, lines 2 to 6 of the specification, the Appellants teach that:

> "The term 'which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient' refers to an increase of NOS expression or activity to levels which would exist in normal healthy endothelial tissue, but not to any enhancement of NOS expression or activity above levels that would exist in normal healthy endothelial tissue."

The Appellants contend that it is well within the skill set of an ordinary practitioner to determine the NOS expression levels that are exhibited by normal healthy endothelial tissues. Such methods are well known in the art and routinely practiced. For instance, Example 5 on page 33, line 20 clearly teaches how endothelial cell NOS expression levels can be measured in healthy tissue and compared to levels within diseased tissue.

Therefore, in view of the teachings of the specification, one of ordinary skill in the art, using routine methods, could determine normal NOS expression levels in healthy endothelial tissue and would clearly understand what would constitute an enhancement of said expression levels above that exist in the healthy tissue. Accordingly, the Applicants contend that the "metes and bounds" of the claims would be clear to one of skill in the art and respectfully request that this rejection be withdrawn.

The Examiner has suggested deletion of the term "substantially". Appellants respectfully submit that the phrase has been given a very specific meaning in the text of the specification, which allows one of skill in the art to clearly understand the intended scope of the claim, and that to delete the word "substantially" would render the phrase without a clear meaning, as the definition provided by Appellants would then no longer be applicable.

Rejections under 35 U.S.C. § 102 (b) over Liao et al.

Claims 1, 3-8, 10, 12, 19-22, 30, 32-33 and 39 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Liao et al. (WO 00/56403). Appellants respectfully submit that the presently claimed invention is novel in view of the cited art.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Additionally, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1566 (Fed. Cir. 1990).

Arguments directed to Claims 1, 3-8, 10, 12 and 19-22

Claim 1 and the claims dependent thereupon, i.e. Claims 3-8, 10, 12-13 and 19-22 are directed to methods of treating a lung proliferative disorder by administering an HMG-CoA reductase inhibitor.

Accordingly, an element of the claims is administering an amount of a HMG-CoA reductase inhibitor that is effective to reduce vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries. The Appellants contend that Liao does not teach this element. Liao does not teach this element because Liao actually teaches a method for increasing endothelial cell nitric oxide synthase activity. See for instance, page 4, lines 21 to 26, below:

> According to one aspect of the invention, a method is provided for increasing endothelial cell Nitric Oxide Synthase activity in a nonhypercholesterolemic subject who would benefit from increased endothelial cell Nitric Oxide Synthase activity in a tissue. The method involves administering to a nonhypercholesterolemic subject in need of such treatment a HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the tissue of the subject.

The requirement for upregulating ecNOS is reiterated throughout the specification, for example at page 4, lines 23-26; page 6, lines 23-25, page 8, lines 5-7, page 5, lines 9-10, and in the claims, where it is specifically recited in, for example, Claims 1 and 5. It is therefore clear that the cited art intends a dose and route of administration of an HMG-CoA reductase that will result in increased ecNOS activity.

Therefore, because Liao actually teaches a method for increasing endothelial cell nitric oxide synthase activity, it teaches a method opposite of what is recited in the Applicants' claims. Hence, Liao does not teach every element of the rejected claims and, consequently, does not anticipate the claimed invention. For this reason alone, this rejection should be reversed.

Additionally, the Appellants would like to draw the attention of the Board to the Court's ruling in SmithKline Beecham, wherein it was held that in order to anticipate a claimed invention a prior art disclosure must be enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation. See SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1342 (Fed. Cir. 2005).

The Appellants contend that given the disclosure set forth in Liao, one of ordinary skill in the art could not practice the Applicants' claimed invention without undue experimentation. One of skill in the art could not practice the Appellants' claimed invention without undue experimentation, in view of Liao, because Liao is directed to administering a HMG-CoA

reductase inhibitor to upregulate endothelial cell NOS (ecNOS) activity and thereby treating a disease condition.

The Appellants' claimed invention is based partially upon the discovery that HMG-CoA reductase inhibitors show efficacy both in (1) preventing the development of smooth muscle cell hyperplasia (including medial hypertrophy), and in (2) inducing apoptosis in diseased and hypertrophied vascular tissues. The Appellants' discovery is in sharp contrast to methods, such as those disclosed in Liao, which teach the administration of HMG-CoA reductase inhibitors to increase expression of ecNOS. As stated in the Appellants' specification at page 10, lines 9 to 24:

> "This discovery is in sharp contrast to earlier ideas postulating that HMG-CoA reductase inhibitors act to increase expression or activity of endothelial cell nitric oxide synthase (NOS), thereby relieving the symptoms of pulmonary hypertension or other vascular disorder by relaxing the vascular smooth muscle cells. Instead, the present applicants show that antiproliferative agents such as HMG-CoA reductase inhibitors are involved in direct resolution of the neointimal smooth muscle hyperplasia and medial hypertrophy that causes the vascular occlusion in disease states associated with lung proliferative vascular disorders. In fact, it is demonstrated herein that antiproliferative agents induce apoptosis of vascular smooth muscle cells, resulting in shrinkage of the tissue and direct resolution of the vascular occlusion. The decrease in vascular occlusion that results is much greater than any vasodilation that could occur from the administration of a vasodilator, even in the presence of normal levels of eNOS."

Accordingly, due to the fact that Liao involves administering a HMG-CoA reductase inhibitor to upregulate endothelial cell NOS activity, the results of which have been questioned[1], and the Applicants' methods involve the administration of a HMG-CoA reductase inhibitor to reverse vascular occlusion by reversing neointimal hyperplasia, and thereby promoting the restoration of normal healthy endothelial cells, the Applicants contend that in view of the teachings of Liao, one of ordinary skill in the art could not practice the claimed invention without undue experimentation. Therefore, for this additional reason Liao et al. is not an appropriate prior art citable under § 102.

In view of the above, the Appellants contend that Claims 1, 3-8, 10, 12 and 19-22 are not anticipated by Liao because Liao fails to teach all the elements of the rejected claims and/or is

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[1] Reports concerning the role of NOS in pulmonary vascular diseases are contradictory. Berger *et al.* stated that it remains uncertain whether impaired endothelium-dependent vasorelaxation is associated with a decrease in NOS activity, and suggested that other alterations in endothelial cell metabolism may be primarily responsible for the impaired vasorelaxation. In short, these authors stated that impaired endothelial-dependent vasorelaxation may occur despite increased NOS activity. (Berger, R, et al. (2001) Am. J. Respir. Crit. Care Med. 163:1493-1499). See page 3, lines 6 to 11.

not enabled with respect to the Appellants' claimed invention. Consequently, the Appellants respectfully request that the 35 U.S.C. § 102(b) rejection be reversed.

Arguments directed to Claim 3

Claim 3 is specifically directed to treating primary pulmonary hypertension in a patient.

Applicants note that Liao *et al.* does not teach a method wherein this goal can be achieved in a patient suffering from a primary pulmonary hypertension. Liao *et al.* provide the very general range of 0.01 mg/kg to 1000 mg/kg as being suitable for administration. However, the reference fails to provide any evidence that such a dose can be administered to an animal for the purpose of treating primary pulmonary hypertension. The examples provided by Liao *et al.* relate to cell culture assays, for example as illustrated in Figures 1-3, which show changes in ecNOS expression *in vitro*, or to cerebral infarction (Figures 4-6). There is no *in vivo* data provided by Liao *et al.* that would direct one of skill in the art in how to treat primary pulmonary hypertension by administering an HMG-CoA reductase inhibitor in a dose that increases ecNOS activity. While Liao *et al.* speculate and assert that this can be achieved; in fact there is no supporting evidence.

In view of the foregoing discussion and the other deficiencies of Liao *et al.* discussed above, the Applicants contend that Claim 3 is not anticipated by Liao *et al.* because Liao *et al.* fails to teach all the elements of the rejected claims and/or is not enabled with respect to the Applicants' claimed invention. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection be reversed.

Arguments directed to Claims 30, 32-33 and 39

Claim 30 and the claims dependent thereupon, i.e. Claims 32, 33, and 39 are directed to a method of reversing right ventricular hypertrophy in a patient suffering from pulmonary hypertension by administering an HMG-CoA reductase inhibitor.

Applicants respectfully submit that there is no mention or teaching of such a treatment in cited art. Before the discovery reported in the instant application, it was highly unexpected that one could achieve an actual reversal of such a serious cardiac disorder. The cited art is completely silent on the subject, and the deficiencies of the art with respect to pulmonary proliferative diseases are even more noticeable on this point.

Applicants respectfully submit that Liao *et al.* fail to teach the recited elements of the claimed invention. Reversal of the rejection is requested.

Rejections under 35 U.S.C. § 103 (a) over Liao et al.

Claims 13, 23-24 and 37 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Liao et al.

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. See, for example:

- *Pharmastem Therapeutics v. Viacell et al.*, 2007 U.S. App. LEXIS 16245 (Fed. Cir. 2007) which states that "the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007));
- *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) which states that "[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (citing KSR Int'l Co. at 1741); and
- *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) which states that "[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (citing In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004)).

Arguments directed to Claim 13

Claim 13 recites the method of Claim 1 and further requires administering prostacyclin.

For the reasons discussed in response to § 102 rejection, Applicants respectfully submit that Liao *et al.* fail to teach a method for treating a lung proliferative disorder wherein the amount of HMG-CoA administered does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient.

As described in the previous section, Liao *et al.* teaches a method for increasing ecNOS activity. The teachings of Liao *et al.* would not lead one of skill in the art to try to find treatment methods that do not substantially increase ecNOS activity as is required by the instant method. As the prior art teaches a dosing and regimen that produces an effect opposite of that taught by Appellants (i.e. where ecNOS is not substantially increased), there is no teaching that would suggest or motivate one of skill in the art to pursue Appellants' invention.

Appellants respectfully submit that the invention of Claim 13 is not made obvious by the cited reference. Reversal of the rejection is requested.

Arguments directed to Claims 23 and 24

Claim 23 and the claim dependent thereupon, i.e. Claim 24, are directed to methods of treating a primary pulmonary hypertension by administering an HMG-CoA reductase inhibitor by inhalation.

An element of Claim 23 is administering a dose of a HMG-CoA reductase inhibitor that is effective to reduce vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries.

Appellants further note, as discussed above, that even for the methods claimed by Liao *et al.*, that is, a method wherein primary pulmonary hypertension is treated by administering an HMG-CoA reductase inhibitor in a dose that increases ecNOS activity, the reference lacks specific guidelines for dose and route of administration whereby one could accomplish the sought after result.

The Office Action states that "those of ordinary skill in the art would have been readily optimized effective delivery forms as determined by good medical practice and the clinical condition of the patient."

Appellants respectfully disagree. In view of this lack of teaching by Liao *et al.* it is not obvious that one should "optimize" effective delivery forms. The process of optimization lacks a credible foundation when the desired result has not yet been obtained, and becomes, instead, a searching for hope of success, without a reasonable expectation that such will be found.

Arguments directed to Claim 37

Claim 37 is directed to methods of treating a primary pulmonary hypertension by administering simvastatin by inhalation.

Liao *et al.* teach a method of treating various diseases by using simvastatin to increase ecNOS activity. Claim 37 is directed to using simvastatin to treat primary pulmonary hypertension by administering simvastatin at a dose and through a delivery route effective to reduce vascular occlusion in the pulmonary arteries of the patient but which does not substantially increase ecNOS activity in the endothelial cells of the pulmonary arteries of the patient.

As discussed in the above sections, Liao *et al.* is teaching a method which is exact opposite of the method taught in claim 37 as in Liao *et al.*' method ecNOS activity is increased while in the instant method ecNOS activity is not substantially increased.

The arguments against Liao *et al.* in making obvious the dose and route of administering simvastatin are applied as above.

The Appellants submit that all aspects of the §103(a) rejection have been addressed and may be reversed. Reversal of this rejection is requested.

SUMMARY

Claims 1, 3-8, 10, 12-13 and 19-24 are not indefinite under 35 U.S.C. § 112, second paragraph.

Claims 1, 3-8, 10, 12, 19-22, 30, 32-33 and 39 are not anticipated by Liao et al. (WO00/56403) under 35 U.S.C. § 102 (b).

Claims 13, 23-24 and 37 are not obvious over Liao et al. (WO00/56403) under 35 U.S.C. § 103 (a).

Relief Requested

The Appellants respectfully request that all rejections of Claims 1, 3-8, 10, 12-13, 19-24, 30, 32-33, 37 and 39 be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,
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CLAIMS APPENDIX

1. A method of treating a lung proliferative vascular disorder in a patient comprising administering an HMG-CoA reductase inhibitor,

wherein the HMG-CoA reductase inhibitor is present in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient, and which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient; and

wherein said lung proliferative vascular disorder is selected from the group consisting of primary pulmonary hypertension, secondary pulmonary hypertension, Eisenmenger's syndrome, chronic thromboembolic disease, pulmonary fibrosis, obliterative bronchiolitis, and lymphangioleiomyomatosis.

2. (Canceled)

3. A method of treating primary pulmonary hypertension in a patient comprising:

administering an HMG-CoA reductase inhibitor in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier at a dose of from about 0.1 to about 100 mg/kg per day, wherein the formulation further comprises in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient, and which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient.

4. The method of claim 1, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pravastatin, pitastatin, rosuvastatin and simvastatin.

5. The method of claim 1, wherein the HMG-CoA reductase inhibitor is simvastatin.

6. The method of claim 1, wherein the HMG-CoA reductase inhibitor is administered in a pharmaceutical formulation at a dose of from about 0.1 to about 100 mg/kg per day.

7. The method of claim 6, wherein the formulation further comprises a pharmaceutically acceptable carrier suitable for oral, parenteral, transdermal, transmucosal, or pulmonary delivery.

8. The method of claim 1, further comprising administering an additional active agent, wherein said additional active agent is selected from the group consisting of anticoagulants, vasodilators, macrolide anti-inflammatory agents, diterpenoid triepoxides, endothelin receptor antagonists, geranyl transferase inhibitors, farnesyl transferase inhibitors, and inhibitors of EGF tyrosine kinase, and pharmaceutically acceptable salts and esters thereof.

9. (Canceled)

10. The method of Claim 8, wherein the additional active agent is a vasodilator selected from the group consisting of prostanoids, phosphodiesterase (PDE) inhibitors, nitric oxide, nitric oxide precursors and calcium channel blockers.

11. (Canceled)

12. The method of 10, wherein the prostanoid is prostacylin, treprostinil, iloprost, beraprost, prostaglandin E_1 or prostaglandin E_2.

13. The method of claim 12, wherein the prostanoid is prostacyclin.

14-18. (Canceled)

19. The method of claim 1, wherein neointimal smooth muscle cell hyperplasia is decreased upon treatment with the HMG-CoA reductase inhibitor, thereby reducing the neointimal smooth muscle cell hyperplasia in the pulmonary arteries of the patient.

20. The method of claim 1, wherein the lung proliferative vascular disorder is characterized by vascular occlusion in the pulmonary arteries of the patient, and wherein the vascular occlusion is reversed upon treatment with the HMG-CoA reductase inhibitor, such that an increase in blood flow is provided through the pulmonary arteries.

21. The method of claim 20, wherein the blood flow is increased by from about 5% to at least about 300%.

22. The method of claim 1, wherein the lung proliferative vascular disorder is characterized by pulmonary hypertension, and wherein the hypertension is reversed upon treatment with the HMG-CoA reductase inhibitor.

23. A method of treating a primary pulmonary hypertension in a patient comprising:

administering an HMG-CoA reductase inhibitor in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier suitable for pulmonary delivery at a dose of from about 0.1 to about 100 mg/kg per day, wherein the formulation further comprises in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient, and which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient;

wherein the HMG-CoA reductase inhibitor is administered by inhalation.

24. The method of claim 23, wherein the HMG-CoA reductase inhibitor is administered using a dry powder inhaler, metered dose inhaler, or nebulizer.

25 – 29. (Canceled)

30. A method of reversing right ventricular hypertrophy in a patient suffering from pulmonary hypertension comprising administering an HMG-CoA reductase inhibitor.

31. (Canceled)

32. The method of claim 30, further comprising administering an additional active agent selected from the group consisting of anticoagulants, vasodilators, macrolide anti-inflammatory agents, diterpenoid triepoxides, inhibitors of EGF tyrosine kinase receptor signaling, geranyl transferase inhibitors, farnesyl transferase inhibitors, and endothelin receptor antagonists, and pharmaceutically acceptable salts and esters thereof.

33. The method of Claim 30, wherein the HMG-CoA reductase inhibitor is simvastatin.

34-36. (Canceled)

37. A method of treating a primary pulmonary hypertension in a patient comprising:

administering simvastatin in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier suitable for pulmonary delivery at a dose of from about 0.1 to about 100 mg/kg per day, wherein the formulation further comprises in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient, and which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient;

wherein the simvastatin is administered by inhalation.

38. (Canceled)

39. The method of claim 33, further comprising administering an additional active agent selected from the group consisting of anticoagulants, vasodilators, macrolide anti-inflammatory agents, FK506, inhibitors of EGF tyrosine kinase receptor signaling, diterpenoid triepoxides, geranyl transferase inhibitors, farnesyl transferase inhibitors, and endothelin receptor antagonists, and pharmaceutically acceptable salts and esters thereof.

EVIDENCE APPENDIX

No evidence submitted under 37 CFR §§ 1.130, 1.131 or 1.132 has been relied upon by Appellant in this Appeal.

RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a court or the Board which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.